Therapeutic combinations and compositions for the treatment of inflammatory bowel disease

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(54) Title: THERAPEUTIC COMBINATIONS AND COMPOSITIONS FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

(57) Abstract: The present invention relates to pharmaceutical combinations of at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and riboflavin to treat patients suffering from inflammatory bowel disease (IBD) or other inflammatory conditions. This invention also relates to additive and/or combinations of at least one thiopurine and riboflavin. This invention is also related to a method for the treatment or prophylaxis of IBD or other inflammatory conditions, which method comprises administering a therapeutically effective amount of thiopurine and riboflavin.

THERAPEUTIC COMBINATIONS AND COMPOSITIONS FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

The present invention relates to pharmaceutical combinations of at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and riboflavin to treat patients suffering from inflammatory bowel disease (IBD) or other inflammatory conditions (such as rheumatoid arthritis, ankylosing spondylitis, psoriasis, lupus erythematous and multiple sclerosis). This invention also relates to additive and/or combinations of at least one thiopurine and riboflavin.
This invention is also related to a method for the treatment or prophylaxis of IBD, which method comprises administering a therapeutically effective amount of thiopurine and riboflavin.

The thiopurine drugs are purine antimetabolites widely used in the treatment of i.e. inflammatory bowel disease (IBD).

Thiopurine covers a range of various active compounds such as:

6-Mercaptopurine (6-MP), which is also known as mercaptopurine is sold i.e. under the brand name Purinethol among others. It is taken by mouth.

Azathioprine (AZA), which is sold under the brand name Imuran among others. It is taken by mouth or injected into a vein.

Thioguanine, which is also known as tioguanine or 6-thioguanine (6-TG) is sold i.e. under the brand name Lanvis among others. It is taken by mouth.

Riboflavin, also known as vitamin B2, is a micronutrient with a key role in maintaining health in humans and other mammals. It is the central component of the cofactors FAD and FMN, and is therefore required by all flavoproteins. As such, riboflavin is required for a wide variety of cellular processes. It plays a key role in energy metabolism, and for the metabolism of fats, ketone bodies, carbohydrates, and proteins. Moreover, riboflavin has anti-inflammatory and anti-oxidant effects. Riboflavin is

found naturally in asparagus, popcorn, bananas, per-simmons, okra, chard, cottage cheese, milk, yogurt, meat, eggs, fish, and green beans. Other sources specify cheese, leafy green vegetables, liver, kidneys, legumes, tomatoes, yeast, mushrooms, and almonds.

Inflammatory Bowel Disease (IBD) is a chronic and debilitating illness. It is characterized by chronic intestinal inflammation that often shows an intermittent course with acute attacks followed by periods of remission. Clinical symptoms during acute attacks include diarrhea, bleeding, abdominal pain, fever, joint pain, and weight loss. These symptoms can range from mild to severe, and may gradually and subtly develop from an initial minor discomfort, or may present themselves suddenly in full-blown form. IBD can manifest itself in a variety of forms, the most common of which are Crohn's disease and ulcerative colitis. Both of these diseases are similar in terms of clinical symptoms, even though their inflammation patterns are distributed differently in the GI tract. Crohn's disease is a chronic transmural inflammation of the bowel, which can affect the whole gastrointestinal tract, usually in a discontinuous pattern. The initial location of CD is most commonly in the lower ileum. From here the inflammation typically spreads towards proximal parts of the small intestine. However, the colon is also often involved.

Ulcerative colitis is a chronic inflammatory bowel disease affecting only the colon and shows a continuous distribution in the gastrointestinal mucosa. In most patients the focal point of the inflammation is in the distal part of the colon and the rectum. From this origin, the inflammation often spreads proximally. In the most severe cases, the whole colon is affected which is called as "pancolitis". About 30% of patients suffer from this severe form of UC.

The present invention relates to a pharmaceutical combination (PC) comprising

(i) at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and

(ii) riboflavin.

The present invention relates to a pharmaceutical combination (PC') comprising

(i) at least one thiopurine and
(ii) riboflavin.

The present invention relates to a pharmaceutical combination (PC'') comprising

(i) at least one pharmaceutically acceptable salt of thiopurine and
(ii) riboflavin.

The present invention relates to a pharmaceutical combination (PC''') comprising

(i) at least one prodrug of thiopurine and
(ii) riboflavin.

The present invention also relates to a pharmaceutical combination (PC''''), which is pharmaceutical combination (PC), (PC'), (PC'') or (PC'''), wherein thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof are chosen from the group consisting of 6-mercaptopurine, azathioprine and thioguanine.

The present invention relates to a pharmaceutical combination (PC1) consisting of

(i) at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and
(ii) riboflavin.

The present invention relates to a pharmaceutical combination (PC1') consisting of

(i) at least one thiopurine and
(ii) riboflavin.

The present invention relates to a pharmaceutical combination (PC1'') consisting of

(i) at least one pharmaceutically acceptable salt of thiopurine and
(ii) riboflavin.

The present invention relates to a pharmaceutical combination (PC1''') consisting of

(i) at least one prodrug of thiopurine and
(ii) riboflavin.

The present invention also relates to a pharmaceutical combination (PC1''''), which is pharmaceutical combination (PC1), (PC1'), (PC1'') or (PC1'''), wherein thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof are chosen from the group consisting of 6-mercaptopurine, azathioprine and thioguanine.

The present invention relates to a formulation (F) comprises pharmaceutical combinations of

(i) at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and
(ii) riboflavin.

The present invention relates to a formulation (F') comprises pharmaceutical combinations of

(i) at least one thiopurine and
(ii) riboflavin.

The present invention relates to a formulation (F'') comprises pharmaceutical combinations of

(i) at least one pharmaceutically acceptable salt of thiopurine and
(ii) riboflavin.

The present invention relates to a formulation (F''') comprises pharmaceutical combinations of

(i) at least one prodrug of thiopurine and
(ii) riboflavin.

The present invention also relates to a formulation (F''''), which is formulation (F), (F'), (F'') or (F'''), wherein thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof are chosen from the group consisting of 6-mercaptopurine, azathioprine and thioguanine.

The present invention also relates to a method (M) for the treatment or prophylaxis of IBD or other inflammatory conditions, which method comprises administering a therapeutically effective amount of

(i) at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and
(ii) riboflavin.

The present invention also relates to a method (M') for the treatment or prophylaxis of IBD or other inflammatory conditions, which method comprises administering a therapeutically effective amount of

(i) at least one thiopurine and
(ii) riboflavin.

The present invention also relates to a method (M'') for the treatment or prophylaxis of IBD or other inflammatory conditions, which method comprises administering a therapeutically effective amount of

(i) at least one pharmaceutically acceptable salt of thiopurine and
(ii) riboflavin.

The present invention also relates to a method (M''') for the treatment or prophylaxis of IBD or other inflammatory conditions, which method comprises administering a therapeutically effective amount of

(i) at least one prodrug of thiopurine and
(ii) riboflavin.

The present invention also relates to a method (M''''), which is method (M), (M'), (M'') or (M'''), wherein thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof are chosen from the group consisting of 6-mercaptopurine, azathioprine and thioguanine.

The present invention also relates to a method (M1) for the treatment of IBD or other inflammatory conditions, which method comprises administering a therapeutically effective amount of

(i) at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and
(ii) riboflavin.

The present invention also relates to a method (M1') for the treatment of IBD or other inflammatory conditions, which method comprises administering a therapeutically effective amount of

(i) at least one thiopurine and
(ii) riboflavin.

The present invention also relates to a method (M1'') for the treatment of IBD or other inflammatory conditions, which method comprises administering a therapeutically effective amount of

(i) at least one pharmaceutically acceptable salt of thiopurine and
(ii) riboflavin.

The present invention also relates to a method (M1''') for the treatment of IBD or other inflammatory conditions, which method comprises administering a therapeutically effective amount of

(i) at least one prodrug of thiopurine and
(ii) riboflavin.

The present invention also relates to a method (M1''''), which is method (M1), (M1'), (M1'') or (M1'''), wherein thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof are chosen from the group consisting of 6-mercaptopurine, azathioprine and thioguanine.

Another embodiment of this invention is a method of treating or lessening the symptoms of inflammatory bowel disease or other inflammatory conditions comprising administering to a person in need thereof an effective amount of at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and riboflavin.

Therefore, the present invention also relates to a method (M2) of treating or lessening the symptoms of inflammatory bowel disease or other inflammatory conditions comprising administering to a person in need thereof an effective amount of

(i) at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and
(ii) riboflavin.

Therefore, the present invention also relates to a method (M2') of treating or lessening the symptoms of inflammatory bowel disease or other inflammatory conditions comprising administering to a person in need thereof an effective amount of

(i) at least one thiopurine and
(ii) riboflavin.

Therefore, the present invention also relates to a method (M2'') of treating or lessening the symptoms of inflammatory bowel disease or other inflammatory conditions comprising administering to a person in need thereof an effective amount of

(i) at least one pharmaceutically acceptable salt of thiopurine and
(ii) riboflavin.

Therefore, the present invention also relates to a method (M2''') of treating or lessening the symptoms of inflammatory bowel disease or other inflammatory conditions comprising administering to a person in need thereof an effective amount of

(i) at least one prodrug of thiopurine and
(ii) riboflavin.

The present invention also relates to a method (M2''''), which is method (M2), (M2'), (M2'') or (M2'''), wherein thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof are chosen from the group consisting of 6-mercaptopurine, azathioprine and thioguanine.

Another embodiment of this invention is the use of the combination of at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and riboflavin to treat or lessen the symptoms of IBD or other inflammatory conditions.

Therefore, the present invention also relates to the use (U) of the combination of

(i) at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and
(ii) riboflavin

to treat or lessen the symptoms of IBD or other inflammatory conditions.
Therefore, the present invention also relates to the use (U') of the combination of

(i) at least one thiopurine and
(ii) riboflavin

to treat or lessen the symptoms of IBD or other inflammatory conditions.

Therefore, the present invention also relates to the use (U'') of the combination of

(i) at least one pharmaceutically acceptable salt of thiopurine and
(ii) riboflavin

to treat or lessen the symptoms of IBD or other inflammatory conditions.

Therefore, the present invention also relates to the use (U''') of the combination of

(i) at least one prodrug of thiopurine and
(ii) riboflavin

to treat or lessen the symptoms of IBD or other inflammatory conditions.

The present invention also relates to a method (U''''), which is use (U), (U'), (U'') or (U'''), wherein thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof are chosen from the group consisting of 6-mercaptopurine, azathioprine and thioguanine.

Another embodiment of this invention is the use of the combination of riboflavin and at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof in the manufacture of a pharmaceutical to treat or lessen the symptoms of IBD.

Therefore, the present invention also relates to the use (U1) of the combination of

(i) at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and
(ii) riboflavin

in the manufacture of a pharmaceutical to treat or lessen the symptoms of IBD or other inflammatory conditions.

Therefore, the present invention also relates to the use (U1') of the combination of

(i) at least one thiopurine and
(ii) riboflavin

in the manufacture of a pharmaceutical to treat or lessen the symptoms of IBD or other inflammatory conditions.

Therefore, the present invention also relates to the use (U1'') of the combination of

(i) at least one pharmaceutically acceptable salt of thiopurine and
(ii) riboflavin

in the manufacture of a pharmaceutical to treat or lessen the symptoms of IBD or other inflammatory conditions.

Therefore, the present invention also relates to the use (U1''') of the combination of

(i) at least one prodrug of thiopurine and
(ii) riboflavin

in the manufacture of a pharmaceutical to treat or lessen the symptoms of IBD or other inflammatory conditions.

The present invention also relates to a method (U1''''), which is use (U1), (U1'), (U1'') or (U1'''), wherein thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof are chosen from the group consisting of 6-mercaptopurine, azathioprine and thioguanine.

Furthermore, the present invention also relates to the pharmaceutical combination (PC), (PC'), (PC''), (PC''') or (PC'''') for the use as medicament.

Furthermore, the present invention also relates to the pharmaceutical combination (PC1), (PC1'), (PC1''), (PC1''') or (PC1'''') for the use as medicament.

Furthermore, the present invention also relates to the formulation (F), (F'), (F''), (F''') or (F'''') for the use as medicament.

Furthermore the present invention also relates to the pharmaceutical combination (PC), (PC'), (PC''), (PC''') or (PC'''') for use in the treatment of IBD or other inflammatory conditions (especially Crohn's disease).

Furthermore the present invention also relates to the pharmaceutical combination (PC1), (PC1'), (PC1''), (PC1''') or (PC1'''') for use in the treatment of IBD or other inflammatory conditions (especially Crohn's disease.

Furthermore the present invention also relates to the formulation (F), (F'), (F''), (F''') or (F'''') for use in the treatment of IBD or other inflammatory conditions (especially Crohn's disease.

The combination of at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and riboflavin results in a synergistic effect.

Alternatively it is also possible due to the effect of these two compounds to lower the amount of at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof. This is great and surprising effect due to known the side effects of the thiopurines (such as flu-like symptoms, arthralgia, gastrointestinal complaints, rash, pancreatitis, hepatotoxicity and myelotoxicity).

Therefore the present invention relates to the preventing and/or lessing the side-effects of thiopurine by administering a combination of at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and riboflavin to a patient.

When using the method for the treatment or prophylaxis of IBD or other inflammatory conditions as disclosed above the sequence of administering the thiopurine (and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof) and riboflavin can vary. It is possible that first the thiopurine is administered and then the riboflavin (or vice versa). It also possible to administer them together (such as i.e. in one Galenical formulation if that is possible). It can also be that the sequence can be thiopurine, riboflavin, thiopurine etc. What is meant is that the sequence of administering can vary.

Also in view of the period of time of the administering in case the two compounds are not administered at the same time. This means there can be a gap of time between taken the thiopurine and then the riboflavin (or vice versa).

Preferably, thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and riboflavin are the sole active ingredients in the formulation. This means that other (auxiliary) ingredients may be present in the formulation, which are needed for this specific formulation. These (auxiliary) ingredients are usually added to get a suitable and stable formulation.

Therefore, the present invention also relates to a formulation (F1), which is formulation (F), (F'), (F''), (F''') or (F''''), wherein the at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and riboflavin are the sole active ingredients in the formulation.

Therefore, the present invention relates to a formulation (F2) comprising a pharmaceutical combination consisting of the following active ingredients:

(i) at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and
(ii) riboflavin.

Therefore, the present invention relates to a formulation (F2') comprising a pharmaceutical combination consisting of the following active ingredients:

(i) at least one thiopurine and
(ii) riboflavin.

Therefore, the present invention relates to a formulation (F2'') comprising a pharmaceutical combination consisting of the following active ingredients:

(i) at least one pharmaceutically acceptable salt of thiopurine and
(ii) riboflavin.

Therefore, the present invention relates to a formulation (F2''') comprising a pharmaceutical combination consisting of the following active ingredients:

(i) at least one prodrug of thiopurine and
(ii) riboflavin.

Preferably the thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof are chosen from the group consisting of 6-mercaptopurine, azathioprine and thioguanine.

Therefore, the present invention also relates to a formulation (F3), which is formulation (F2), (F2'), (F2'') or (F2'''), wherein the thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof are chosen from the group consisting of 6-mercaptopurine, azathioprine and thioguanine.

Therefore, the present invention also relates to a formulation (F3'), which is formulation (F2), (F2'), (F2'') or (F2'''), comprising a pharmaceutical combination consisting of the following active ingredients:

(i) 6-mercaptopurine and/or a pharmaceutically acceptable salt and/or at least one prodrug thereof and

(ii) riboflavin.

Therefore, the present invention also relates to a formulation (F3''), which is formulation (F2), (F2'), (F2'') or (F2'''), comprising a pharmaceutical combination consisting of the following active ingredients:

(i) azathioprine and/or a pharmaceutically acceptable salt and/or at least one prodrug thereof and

(ii) riboflavin.

Therefore, the present invention also relates to a formulation (F3'''), which is formulation (F2), (F2'), (F2'') or (F2'''), comprising a pharmaceutical combination consisting of the following active ingredients:

(i) thioguanine and/or a pharmaceutically acceptable salt and/or at least one prodrug thereof and

(ii) riboflavin.

A further embodiment of the present invention is to prepare a formulation (F), (F'), (F''), (F'''), (F''''), (F1), (F2), (F2'), (F2''), (F2'''), (F3), (F3'), (F3''), and/or (F3''').

These pharmaceutical combinations and/or formulations can be used as such, as a premix as well in any suitable galenical formulation.

Therefore, the present invention also relates to a galenical formulation (GF) comprising a formulation (F), (F'), (F''), (F'''), (F''''), (F1), (F2), (F2'), (F2''), (F2''), (F3), (F3'), (F3''), and/or (F3''').

A further embodiment of the present invention is treatment or lessening of IBD or other inflammatory conditions.by the administration a formulation (F), (F'), (F''), (F'''), (F''''), (F1), (F2), (F2'), (F2''), (F2''), (F3), (F3'), (F3''), and/or (F3''').

A further embodiment of the present invention is the treatment of IBD or other inflammatory conditions by the administration a galenical formulation (GF).

As stated above the present invention also related to a method (M) for the treatment or prophylaxis of IBD or other inflammatory conditions., which method comprises administering a therapeutically effective amount of

(i) at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and
(ii) riboflavin.

When using azathioprine, it may also be that azathioprine is in a Galenical form, which is to be injected into a vein. In that case riboflavin can either be added to this Galenical form, or riboflavin can be administered orally.
But the method according to the present invention does not exclude that the two compounds have to administered in the same way (i.e. both orally).

It also possible to administer the least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and the riboflavin separately, wherein the administration of the least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and the riboflavin should take place in an appropriate time period. When the administration is taken place by separate administration of the least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and the riboflavin, the sequence of

the administration is not essential, which means the least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof could be administrated first and then riboflavin or vice versa.

Thiopurine can be used in the dose range of about 0.2 mg/kg bodyweight to about 2.5 mg/kg bodyweight per day and riboflavin can be used in a suitable dose range of 1 mg to 500mg (preferably 30mg – 300mg) per day which can be administered once a day or several times a day.

The dosage vary for the various thiopurines.

For 6-mercaptopurine the dose ranges of from about 1 mg/kg bodyweight to about 1.5mg/kg bodyweight per day, for azathioprine the dose ranges of from about 2.0 mg/kg bodyweight to about 2.5 mg/kg bodyweight per day and for thioguanine the dose ranges of from about 0.2 mg/kg bodyweight to about 0.3 mg/kg bodyweight per day

Therefore, the present invention relates to a daily dosage unit (DDU) comprising 0.2 mg/kg bodyweight to 2.5 mg/kg bodyweight of thiopurine and 1 mg to 500mg (preferably 30mg – 300mg) of riboflavin.

The daily dosage unit means that the amount of the active ingredients (thiopurine and riboflavin) can be taken once a day or more than once a day.

Thiopurine can be used in the dose range of about 0.2 mg/kg bodyweight to about 2.5 mg/kg bodyweight per day and riboflavin can be used in a suitable dose range of 1 mg to 500mg (preferably 30mg – 300mg) per day which can be administered once a day or several times a day.

The dosage vary for the various thiopurines.

For 6-mercaptopurine the dose ranges of from about 1 mg/kg bodyweight to about 1.5mg/kg bodyweight per day, for azathioprine the dose ranges of from about 2.0 mg/kg bodyweight to about 2.5 mg/kg bodyweight per day and for thioguanine the dose ranges of from about 0.2 mg/kg bodyweight to about 0.3 mg/kg bodyweight per day

Therefore, the present invention relates to a daily dosage unit (DDU1) comprising 2 mg/kg bodyweight to 2.5 mg/kg bodyweight of azathioprine and 1 mg to 500mg (preferably 30mg – 300mg) of riboflavin.

Therefore, the present invention relates to a daily dosage unit (DDU2) comprising 1 mg/kg bodyweight to 1.5 mg/kg bodyweight of 6-mercaptopurine and 1 mg to 500mg (preferably 30mg – 300mg) of riboflavin.

Therefore, the present invention relates to a daily dosage unit (DDU3) comprising 0.2 mg/kg bodyweight to 0.3 mg/kg bodyweight of thioguanine and 1 mg to 500mg (preferably 30mg – 300mg) of riboflavin.

These dosage units are usually in a form as describe below as galenical formulations.

Once a day means the dosage form(s) to be taken only one time in 24 hours by which the drug concentration is maintained for whole day in the body.

Several time a day means the dosage form(s) to be taken several times in 24 hours.

It may also be possible to have dosage units for 2 days, 3 days, 4 days, 5 days, 6 days or weekly dosage units.

The galenical formulation can comprise any pharmaceutically acceptable auxiliary agents, which are necessary, needed or desired to form such a galencial formulation. The galencial formulation can be in any form, which is suitable for a patients. Most commonly it is in a solid form (such as a tablet, granules, globuli, powder or similar).

By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable.

Pharmaceutically acceptable excipients include but are not limited to binders, diluents, lubricants, glidants and surface-active agents.

Such pharmaceutically acceptable excipients are used when thiopurine and riboflavin are integrated into a suitable form for administration.

The amount of additive employed will depend upon how much active agent is to be used. One excipient can perform more than one function.

Binders include, but are not limited to, starches such as potato starch, wheat starch, corn starch; microcrystalline cellulose; celluloses such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose (HPMC), ethyl cellulose, sodium carboxy methyl cellulose; natural gums like acacia, alginic acid, guar gum; liquid glucose, dextrin, povidone, syrup, polyethylene oxide, polyvinyl pyrrolidone and the like and mixtures thereof.

Fillers or diluents, which include, but are not limited to confectioner's sugar, compressible sugar, dextrates, dextrin, dextrose, fructose, lactitol, mannitol, sucrose, starch, lactose, xylitol, sorbitol, talc, microcrystalline cellulose, calcium carbonate, calcium phosphate dibasic or tribasic, calcium sulphate, and the like can be used.

Lubricants may be selected from, but are not limited to, those conventionally known in the art such as Mg, Al or Ca or Zn stearate, polyethylene glycol, glyceryl behenate, mineral oil, sodium stearyl fumarate, stearic acid, hydrogenated vegetable oil and talc.

Glidants include, but are not limited to, silicon dioxide; magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate, calcium silicate, magnesium silicate, colloidal silicon dioxide, silicon hydrogel and other materials known to one of ordinary skill in the art.

The pharmaceutical formulation (which are oral dosage forms) according to the present invention include but is not limited to tablets (single layered tablets, multilayered tablets, MUPS, mini tablets, bioadhesive tablets, caplets, matrix tablets, tablet within a tablet, mucoadhesive tablets, modified release tablets, pulsatile release tablets,

timed release tablets), pellets, beads, granules, sustained release formulations, capsules, microcapsules, tablets in capsules and microspheres, matrix formulations, microencapsulation and powder/pellets/granules for suspension.

The galenical formulation of the invention can optionally have one or more coatings such as film coating, sugar coating, enteric coating, bioadhesive coating and other coatings known in the art. These coatings help pharmaceutical formulations to release the drug at the required site of action. In one example, the additional coating prevents the dosage from contacting the mouth or esophagus. In another example, the additional coating remains intact until reaching the small and or large intestine (e.g., an enteric coating). Premature exposure of a bioadhesive layer or dissolution of a pharmaceutical dosage form in the mouth can be prevented with a layer or coating of hydrophilic polymers such as HPMC or gelatin. Optionally, Eudragit FS 3OD or other suitable polymer may be incorporated in coating composition to retard the release of the drug to ensure drug release in the colon.

These coating layers comprises one or more excipients selected from the group comprising coating agents, opacifiers, taste-masking agents, fillers, polishing agents, coloring agents, antitacking agents and the like.

The galenical formulations of the invention can be coated by a wide variety of methods. Suitable methods include compression coating, coating in a fluidized bed or a pan and hot melt (extrusion) coating. Such methods are well known to those skilled in the art.

Non-permeable coatings of insoluble polymers, e.g., cellulose acetate, ethylcellulose, can be used as enteric coatings for delayed/modified release (DR/MR) by inclusion of soluble pore formers in the coating, e.g., PEG, PVA, sugars, salts, detergents, triethyl citrate, triacetin, etc.

Also, coatings of polymers that are susceptible to enzymatic cleavage by colonic bacteria are another means of ensuring release to distal ileum and ascending colon. Ma-

terials such as calcium pectinate can be applied as coatings to dosage form and multiparticulates and disintegrate in the lower gastrointestinal tract, due to bacterial action. Calcium pectinate capsules for encapsulation of bioadhesive multiparticulates are also available.

The pharmaceutical compositions of the present invention can optionally include one or more solubilizers, i.e., additives to increase the solubility of the pharmaceutical active ingredient or other composition components in the solid carrier. Suitable solubilizers for, use in the compositions of the present invention include: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol, available commercially from BASF under the trade name Tetraglycol) or methoxy PEG (Union Carbide); amides, such as 2- pyrrolidone, 2-piperidone, ε-caprolactam, N-alkylpyrrolidone, N- hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide, and polyvinylpyrrolidone; esters, such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ε -caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide (Arlasolve DMI (ICI)), N-methyl pyrrolidones (Pharmasolve (ISP)), monooctanoin, diethylene glycol monoethyl ether (available from Gattefosse under the trade name Transcutol), and water.

Preferred solubilizers include triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide,N-methylpyrrolidone,N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-600, glycofurol, transcutol, propylene glycol, and dimethyl iso-

sorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, SLS, polyethylene glycols glycofurol and propylene glycol. Cyclodextrins polyoxomers, surfactants and like.

Very suitable pharmaceutically acceptable excipients are (pregelatinized) starches (maize, potatoe), lactose (monohydrate), stearic acid, magnesium stearates, methoxyhydroxylpropyl cellulose, polyethylene glycol (such as polyethylene glycol 400) gum accia and (purified) water.

Therefore the present invention relates a galenical formulation (GF') comprising a formulation (F), (F'), (F''), (F'''), (F''''), (F1), (F2), (F2'), (F2''), (F2''), (F3), (F3'), (F3''), and/or (F3''') in the form of tablet, granule, globuli, or powder comprising at least one pharmaceutically acceptable excipient chosen from the group consisting of (pregelatinized) starches (maize, potatoe), lactose (monohydrate), stearic acid, magnesium stearates, methoxyhydroxylpropyl cellulose, polyethylene glycol (such as polyethylene glycol 400) gum accia and (purified) water.

All formulations as well as the galenical formulation described and disclosed above can be produced by using well-known methods and processes.

Examples

In a prospective clinical intervention study, 70 CD patients were included and divided into two groups with (active) and without (quiescent) evidence of mucosal inflammation (defined by fecal calprotectin (FC) cut-off value: 200 µg/g). Patients received 100 mg riboflavin daily for 3 weeks. Clinical disease activity (Harvey-Bradshaw Index: HBI), inflammatory biomarkers (including interleukin 2) as well as fecal microbial composition (including pathogenic Enterobacteriaceae including E. coli) were analyzed before and after riboflavin intervention.

Surprisingly, we found that riboflavin supplementation further reduced clinical disease activity (HBI) in patients with thiopurine treatment (particularly in patients with quiescent disease), however, this was not the case (not as pronounced as) in patients with mesalazine treatment (Figure 1 and Figure 2).

These effects were accompanied by a further reduction in proinflammatory cytokine IL2 as well as in *Enterobacteriaceae* including *E. coli* in patients with thiopurine treatment, in contrast to patients on mesalazine treatment (figures 3 and 4)

Claims

1. A pharmaceutical combination comprising

(i) at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and

(ii) riboflavin.

2. Pharmaceutical combination according to claim 1, comprising

(i) at least one thiopurine and

(ii) riboflavin.

3. Pharmaceutical combination according to claim 1, comprising

(i) at least one pharmaceutically acceptable salt of thiopurine and

(ii) riboflavin.

4. Pharmaceutical combination according to claim 1, comprising

(i) at least one prodrug of thiopurine and

(ii) riboflavin.

5. A pharmaceutical combination consisting of

(i) at least one thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof and

(ii) riboflavin.

6. Pharmaceutical combination according to claim 5, consisting of

(i) at least one thiopurine and

(ii) riboflavin.

7. Pharmaceutical combination according to claim 5, consisting of

(i) at least one pharmaceutically acceptable salt of thiopurine and
(ii) riboflavin.

8. Pharmaceutical combination according to claim 5, consisting

(i) at least one prodrug of thiopurine and
(ii) riboflavin.

9 Pharmaceutical combination according any of the preceding claims, wherein wherein thiopurine and/or at least a pharmaceutically acceptable salt and/or at least one prodrug thereof are chosen from the group consisting of 6-mercaptopurine, azathioprine and thioguanine.

10. Use of the pharmaceutical combination according to any of the preceding claims 1 - 9 to treat or lessen the symptoms of IBD or other inflammatory conditions.

11. Pharmaceutical combination according to any of the preceding claims 1 – 9 for the use as medicament.

12. Pharmaceutical combination according to any of the preceding claims 1 – 9 for use in the treatment of IBD or other inflammatory conditions (especially Crohn's disease).

Figure 1

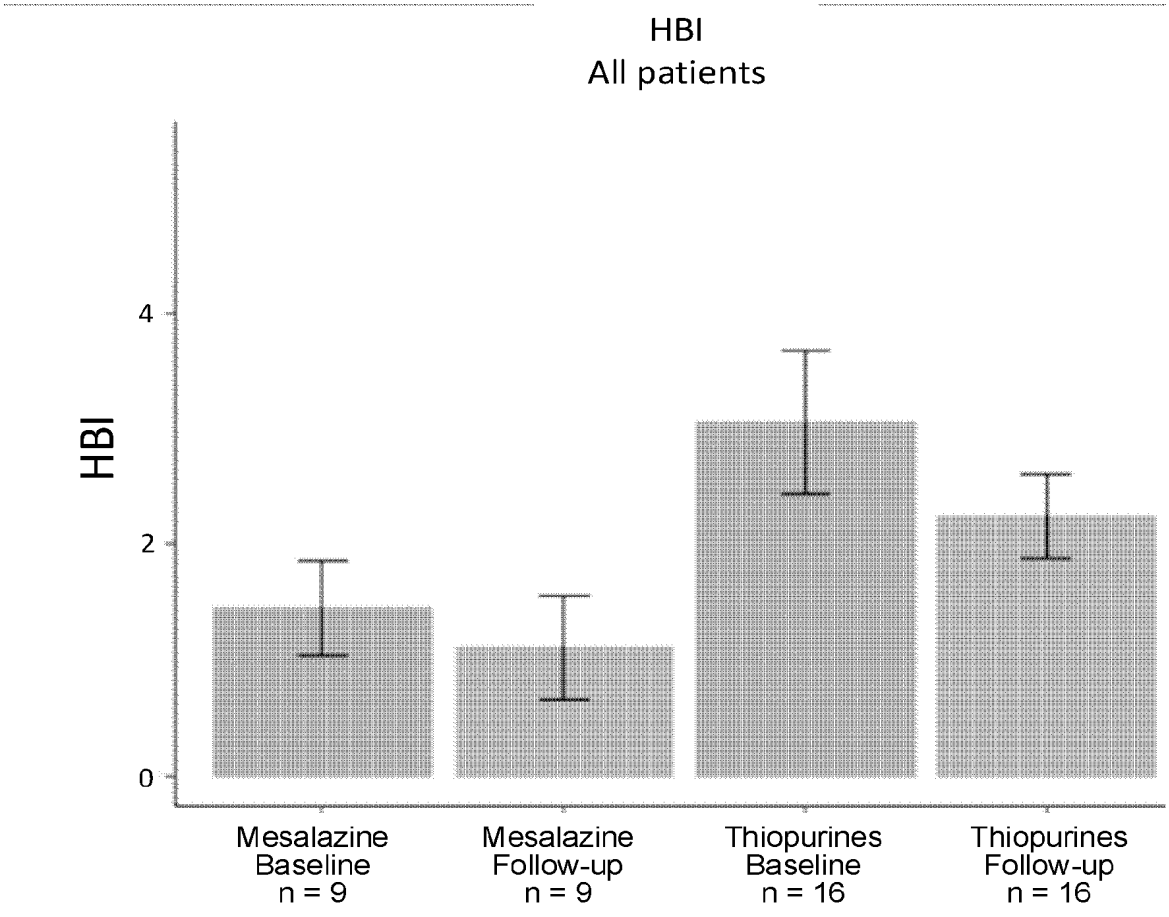

HBI
All patients
HBI
4
2
0
Mesalazine Baseline n = 9
Mesalazine Follow-up n = 9
Thiopurines Baseline n = 16
Thiopurines Follow-up n = 16

Figure 2

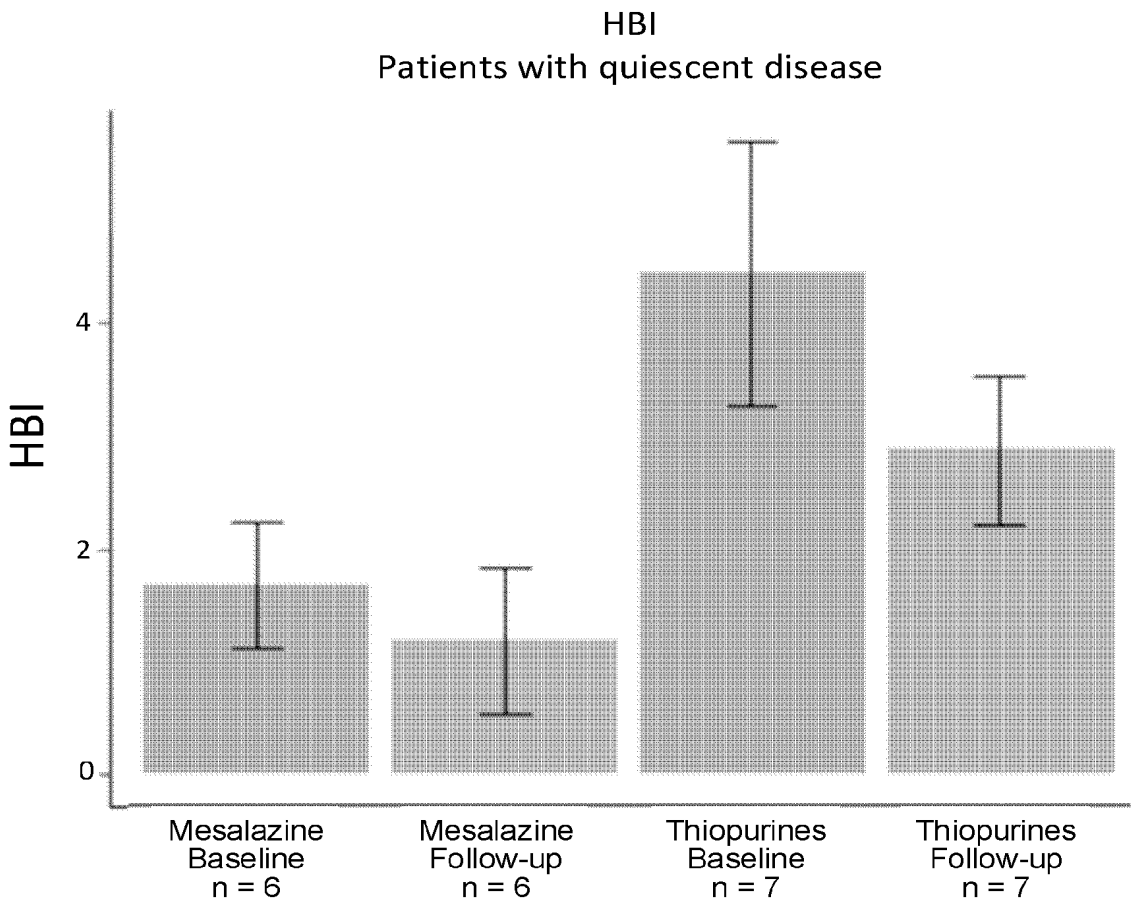
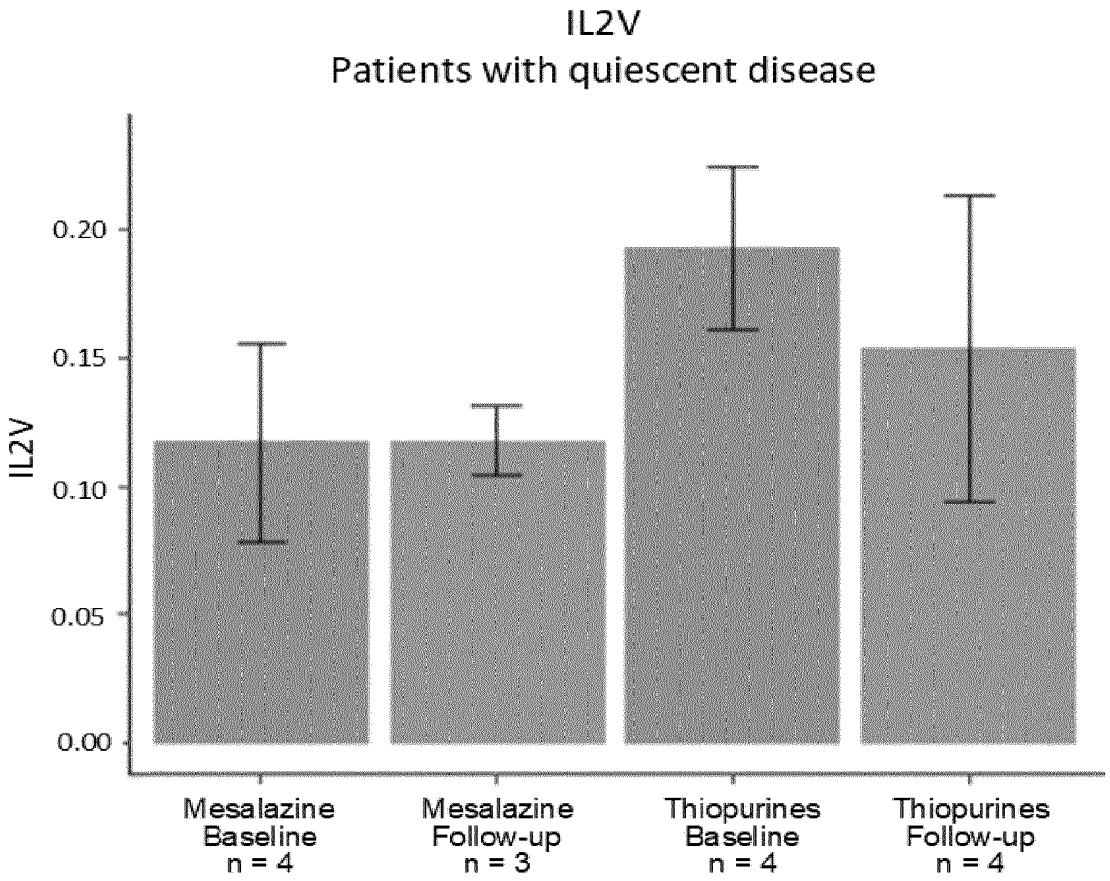
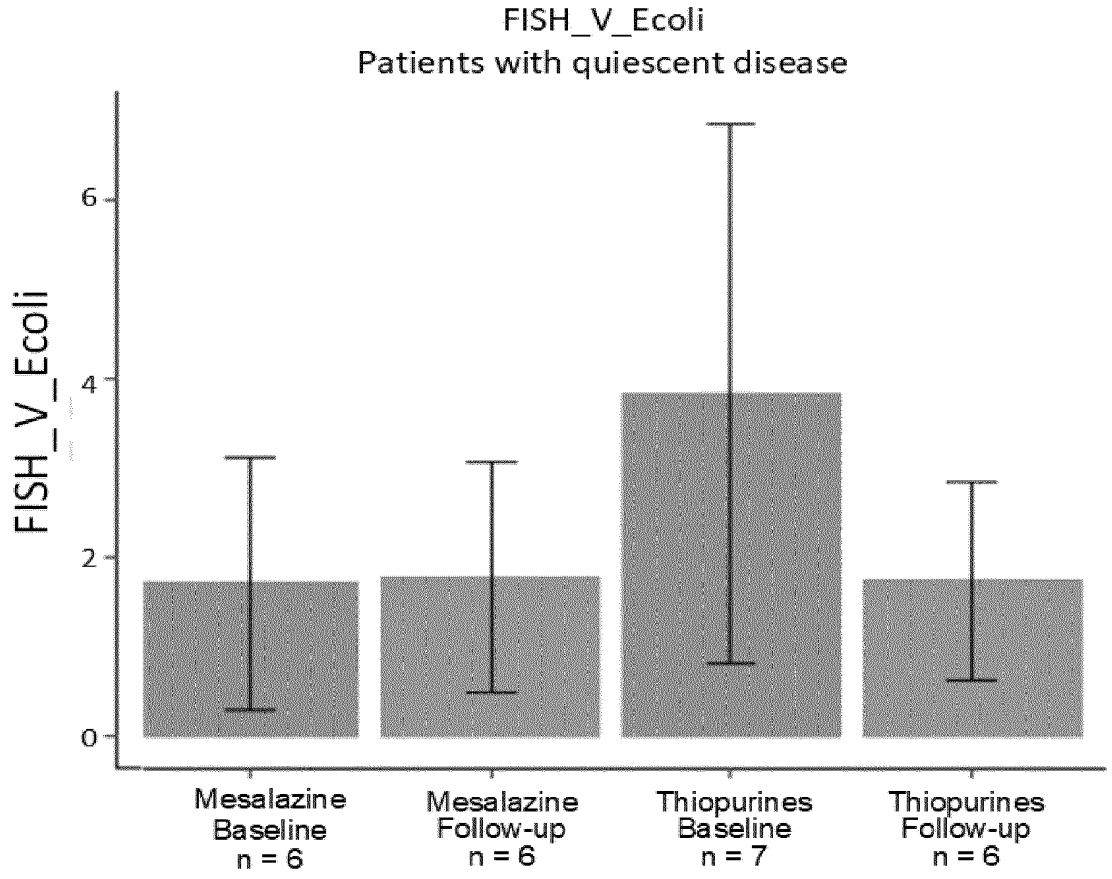

HBI
Patients with quiescent disease
HBI
4
2
0
Mesalazine Baseline n = 6
Mesalazine Follow-up n = 6
Thiopurines Baseline n = 7
Thiopurines Follow-up n = 7

Figure 3


IL2V
Patients with quiescent disease
IL2V
0.20
0.15
0.10
0.05
0.00
Mesalazine Baseline n = 4
Mesalazine Follow-up n = 3
Thiopurines Baseline n = 4
Thiopurines Follow-up n = 4

5

Figure 4


FISH_V_Ecoli
Patients with quiescent disease
FISH_V_Ecoli
0
2
4
6
Mesalazine Baseline n = 6
Mesalazine Follow-up n = 6
Thiopurines Baseline n = 7
Thiopurines Follow-up n = 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/052649

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/52 A61K31/525 A61P1/00 A61P29/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CORINA HARTMAN ET AL: "Food Intake Adequacy in Children and Adolescents With Inflammatory Bowel Disease :", JOURNAL OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION, vol. 63, no. 4, 1 October 2016 (2016-10-01), pages 437-444, XP055609258, US ISSN: 0277-2116, DOI: 10.1097/MPG.0000000000001170	1-4,9-12
Y	page 438, right-hand column, paragraph 3 figure 1d; tables 3,4	1-12

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 April 2020	20/04/2020

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/052649

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 201877 Thomson Scientific, London, GB; AN 2018-783950 XP002793232, -& KR 2018 0106645 A (ASAN FOUND) 1 October 2018 (2018-10-01) abstract -----	1-4,9,11
Y	R. LEVIT ET AL: "Effect of riboflavin-producing bacteria against chemically induced colitis in mice", JOURNAL OF APPLIED MICROBIOLOGY., vol. 124, no. 1, 18 December 2017 (2017-12-18), pages 232-240, XP055496449, GB ISSN: 1364-5072, DOI: 10.1111/jam.13622 page 233, right-hand column, last paragraph page 235, left-hand column, last paragraph - right-hand column, last paragraph figures 2,4,5 page 238, left-hand column, paragraph 2 - page 239, left-hand column, paragraph 3 -----	1-12
X,P	WO 2019/234154 A1 (DSM IP ASSETS BV [NL]) 12 December 2019 (2019-12-12) page 2, paragraph 2 page 3, paragraph 3 -----	1-12

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2020/052649

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
KR 20180106645 A	01-10-2018	NONE	
WO 2019234154 A1	12-12-2019	NONE	